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White Matter Hyperintensity Burden and Susceptibility to Cerebral Ischemia

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Background and Purpose—White matter hyperintensity (WMH) burden increases risk of ischemic stroke; furthermore, it predicts infarct growth in acute cerebral ischemia. We hypothesized that WMH would be less severe in patients with TIA as compared to those with acute ischemic stroke and completed infarct.

Methods—Cases (TIA, n=30) and controls (acute ischemic stroke, n=120) were selected from an ongoing longitudinal cohort study of patients with stroke and matched for age, gender, and race/ethnicity. All subjects had brain MRI within 48 hours of presentation to evaluate for evidence of acute cerebral ischemia. WMH burden on MRI was quantified using a validated computer-assisted program with high inter-rater reliability.

Results—Median WMH volume in individuals with TIA was 3.7 cm³ (interquartile range, 1.5–8.33 cm³) compared to 6.9 cm³ (interquartile range, 3.1–11.9 cm³) in acute ischemic stroke ($P<0.04$). In multivariable analysis, the odds of completed infarct were higher (OR, 2.19; 95% CI, 1.27–3.77; $P<0.005$) in subjects with larger volumes of WMH.

Conclusions—WMH burden was significantly less in subjects with TIA as opposed to those with ischemic stroke. These data provide further evidence to support a detrimental role of WMH burden on the capacity of cerebral tissue to survive acute ischemia. (*Stroke*. 2010;41:00-00.)

Key Words: acute cerebral infarction ■ leukoaraiosis ■ risk factors ■ stroke ■ transient ischemic attack

TIA is diagnosed when neurological dysfunction caused by focal cerebrovascular ischemia does not result in permanent cerebral infarction.¹ Previous definitions of TIA that relied on time limits are now widely considered arbitrary,^{2–4} and in the new American Heart Association-endorsed definition, confirmation of cerebral tissue infarction with imaging is required for final diagnosis.¹

TIA has been studied extensively as a predictor of short-term and long-term risk of ischemic stroke.^{5–7} Risk factors for development of completed infarction in patients with transient symptoms include age, clinical signs of focal weakness or speech impairment, duration of the symptoms, and presence of diabetes mellitus (DM) or hypertension (HTN) on initial evaluation.^{5,8,9} However, there are limited data available to date on neuroimaging determinants of brain tissue susceptibility to ischemia, and progression to cerebral infarct.^{10–12}

In patients with acute ischemic stroke (AIS), severity of leukoaraiosis measured on MRI as white matter hyperintensity volume (WMHV) is associated with progression of initially ischemic cerebral tissue to infarct independent of initial insult size, age, admission blood glucose, admission blood pressure, and stroke subtype.¹⁰ As a marker of chronic

cerebrovascular injury, WMH burden may signify a diminished capacity of cerebral tissue to withstand ischemia.

We hypothesized that WMH would be less severe in patients with TIA as compared to those with AIS and completed infarction, possibly reflecting a greater capacity of cerebral tissue to withstand the acute ischemic injury. We performed a nested case-control study to determine whether the volume of WMH measured on brain MRI differed between the patients with TIA and AIS.

Subjects and Methods

Patient Selection and Definitions

Cases and controls for this nested study were selected from a prospective cohort of consecutive patients aged 18 years or older admitted to our stroke unit through the emergency department between January 2005 and May 2009.¹³ The Institutional Review Board approved all aspects of this study, and informed consent for collection of data was provided by all subjects.

Cases were consenting subjects who presented to the emergency department for evaluation of suspected acute stroke and whose final diagnosis was TIA. TIA was defined as “a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction.”¹ Diffusion-weighted imaging (DWI) MRI completed within 48 hours after symptom onset was used to evaluate for the presence of an acute cerebral infarct.

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Subjects with no DWI findings of acute cerebral infarction and symptom resolution within 24 hours from symptom onset were considered "TIA cases."

All patients were admitted to our stroke unit, where their diagnosis and management were supervised by a vascular neurologist. TIA mimics were ruled out through extensive clinical evaluation, neuroimaging, laboratory and electroencephalographic testing, as indicated.

Controls were subjects selected from the same cohort who presented for evaluation of acute stroke and showed evidence of acute cerebral infarction on DWI. They were matched to cases by age, gender, and race/ethnicity in a 4:1 ratio. Ischemic stroke was defined as a clinical syndrome associated with a radiographically proven acute infarct consistent with a vascular pattern of involvement and without radiographic evidence of a demyelinating or neoplastic disease or other structural disease, including vasculitis, subacute bacterial endocarditis, vasospasm attributable to subarachnoid hemorrhage or cocaine abuse, or primary intracerebral hemorrhage.

Data Collection

All patients were evaluated by a neurologist in the emergency department, where the NIHSS score was determined, all laboratory values were measured, and clinical information was abstracted prospectively by patient or proxy interview and/or supplemented through medical chart review. Time of stroke or TIA was defined as time when a subject or proxy reported acute onset of a neurological deficit or the subject was last known to be well. Vascular risk factors including HTN, DM, hyperlipidemia (HL), coronary artery disease, and atrial fibrillation were coded based on international guidelines as previously described.¹³ Recorded medication use before admission included antiplatelet (aspirin, clopidogrel, aspirin/extended-release dipyridamole, or combination), antihypertensive, and oral hypoglycemic agents, as well as warfarin and statins.

Neuroimaging Analysis

MR images were acquired on 1.5-Tesla Signa scanners (GE Medical Systems) and converted to Analyze format using MRIcro software (University of Nottingham School of Psychology, Nottingham, UK; www.mricro.com) for computer-assisted determination of WMHV. Using a previously published semi-automated method with high inter-rater reliability,^{14,15} WMH maps were created using axial T2 fluid-attenuated inversion recovery sequences aligned with corresponding DWI sequences for exclusion of acute ischemia, edema, and chronic territorial infarcts. Total WMHV was calculated by doubling the WMHV in the hemisphere unaffected by the stroke and was adjusted for head size, as previously described.^{14,16,17} All images in this study were assessed by 3 investigators (N.S.R., K.F., A.K.), with the sample intraclass correlation coefficient for WMHV equal to 0.97.

Statistical Analysis

Statistical analyses were performed using STATA 10.0 (StataCorp LP, College Station, Tex). Continuous variables were expressed as mean±SD with the exception of WMHV, which was expressed as median±interquartile range. Cases and controls were compared in univariate analyses using *t* test, Wilcoxon rank-sum test, and χ^2 test, as appropriate.

Independent predictors of AIS vs TIA were identified using multivariable logistic regression. The final model, which included WMHV, HL, and statin use, was derived using forward selection/backward elimination with threshold inclusion $P<0.2$ and exclusion $P>0.05$. Sensitivity analysis for statin use–HL subgroup was completed by including the categories of "no HL/no statin use," "no HL/statin use," "HL/no statin use," and "HL/statin use" into the final multivariable logistic regression model. Significance was set at 2-sided $P<0.05$.

Results

Of 1135 consenting subjects with symptoms of acute cerebral ischemia and MRI available on admission, 675 (60%) had

Table 1. Clinical Characteristics of the Subjects With Transient Ischemic Attack (n=30) and Acute Ischemic Stroke (n=120)

	TIA	AIS	P Value
Age, y, mean (SD)	64.9 (16.0)	64.7 (15.2)	0.95
Gender, % female	48	48	0.99
Time to MRI>24 hours, %	0.10	0.09	0.52
Admission NIHSS, median (IQR)	4 (2–7)	3 (1–9)	0.81
WMHV, cm ³ , median (IQR)	3.7 (1.5–8.3)	6.9 (3.1–11.9)	0.03
Risk factors, %			
Hypertension	77	71	0.62
Diabetes mellitus	23	24	0.99
Hyperlipidemia	71	47	0.03
Atrial fibrillation	10	24	0.16
Myocardial infarction	6	8	0.99
Antiplatelet agent use*	61	56	0.65
Anticoagulation use*	6	4	0.63
Statin use	58	10	0.0001
Antihypertensive agent use	74	73	0.99
Hypoglycemic agent use	19	23	0.79

IQR indicates interquartile range; NIHSS, National Institutes of Health Stroke Scale; WMHV, white matter hyperintensity volume.

*Pooled analysis (antiplatelet and anticoagulant agent use); P value <0.21 .

WMH quantified. Among these, 93 (14%) were initially presumed to be TIA based on symptom resolution and negative DWI; however, after excluding TIA mimics, only 30 had a final diagnosis of TIA. Median duration of symptoms was 20 minutes (interquartile range, 10–60 minutes). Cases were matched by age, gender, and race/ethnicity with 120 AIS controls (Table 1). There was no difference between the selected controls and the remainder of the AIS cohort by demographics, baseline clinical characteristics, and severity of WMH (all $P>0.2$). Among controls, severity of neurological dysfunction as measured by the admission NIHSS score was mild (median NIHSS, 3; interquartile range, 1–9), with stroke subtype distribution as follows: 10% small vessel, 19% large vessel, 38% cardioembolic, 22% unknown, and 11% other subtype. Two TIA cases (6.6%) vs 10 AIS controls (7.5%) received treatment with intravenous tissue plasminogen activator.

Individuals with TIA had WMH volumes that were smaller compared to those of patients with stroke (median WMHV 3.7 cm³ vs 6.9 cm³; $P<0.04$; Figure). In addition, TIA cases had higher rates of HL (71% vs 47%; $P=0.03$) and statin use (58% vs 10%; $P<0.0001$) before admission. Time to MRI, NIHSS score, rates of comorbidities (including HTN, DM, atrial fibrillation, coronary artery disease, and MI) as well as use of antihypertensive, hypoglycemic, or antithrombotic agents did not differ significantly between the 2 groups (Table 1).

In multivariable analysis, the odds of AIS vs TIA were increased in individuals presenting with greater burden of WMH (OR, 2.19; 95% CI, 1.27–3.77; $P<0.005$; Table 2). In the same model, the odds of AIS vs TIA were lower in those individuals with HL (OR, 0.28; 95% CI, 0.09–0.84; $P=0.02$) or using statins (OR, 0.18; 95% CI, 0.06–0.52; $P=0.002$);

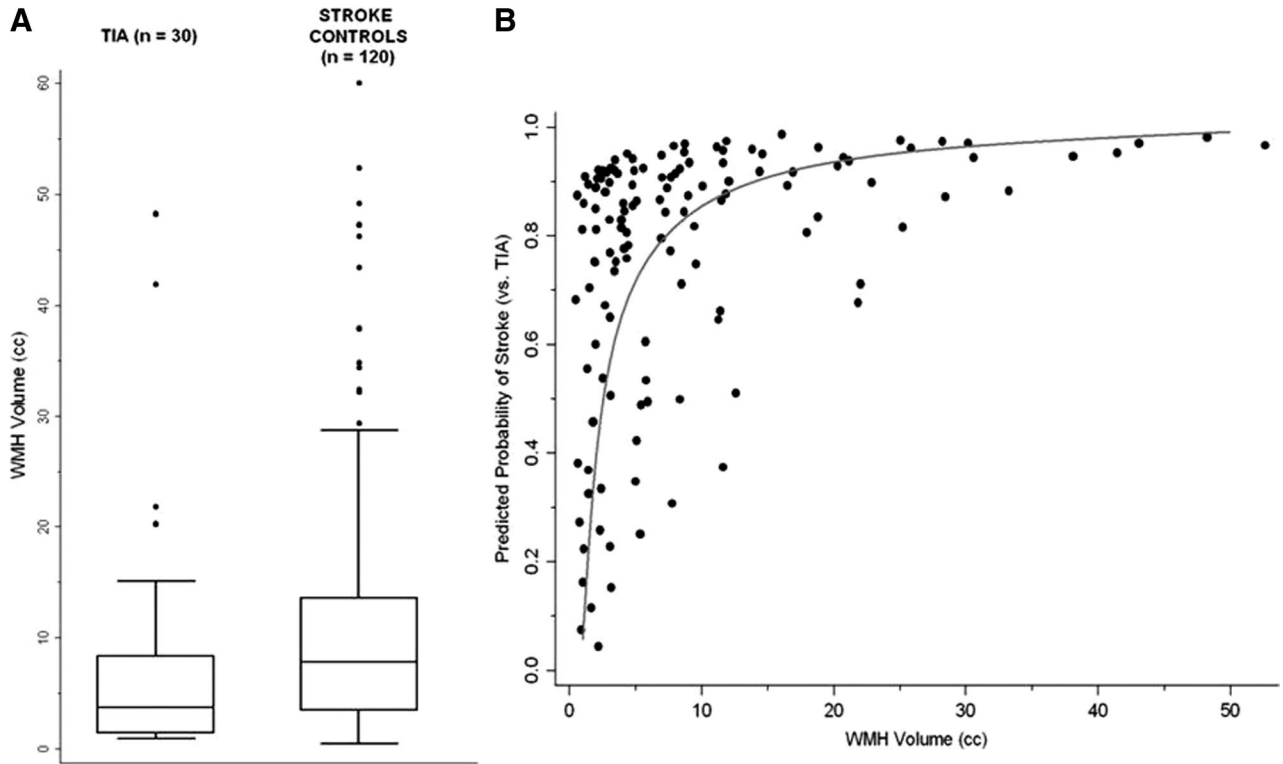


Figure. Severity of white matter hyperintensity (WMH) burden in patients with TIA vs acute ischemic stroke. Burden of leukoaraiosis measured as WMH volume in patients with TIA is significantly less as compared to those with acute ischemic stroke (A). Greater WMH volume measured on admission brain MRI increases the probability of a cerebrovascular infarct (acute ischemic stroke) over that of TIA (B).

however, as expected, colinearity between the diagnosis of HL and statin use was significant ($P < 0.005$). In a sensitivity analysis including WMHV and categories of HL/statin use, odds of AIS vs TIA were significantly lower (OR, 0.27; 95% CI, 0.05–0.47; $P < 0.001$) only in those individuals with combination of HL and statin use. In the same analysis, greater WMHV remained an independent predictor of AIS vs TIA (Table 3).

Discussion

These data from a nested case-control study drawn from a prospective, hospital-based cohort of patients presenting for evaluation of acute ischemic stroke suggest that preexisting injury to the brain as measured by MR-detectable WMH burden may be associated with a diminished capacity of the cerebral tissue to withstand acute ischemia. The burden of WMH was greater in patients who went on to have an acute cerebral infarct as compared to those patients whose cerebrovascular ischemia was transient. Furthermore, greater volumes of WMH independently predicted the probability of the

cerebrovascular event being a stroke as opposed to TIA (Figure).

These findings suggest that the brain’s intrinsic capacity to withstand cerebrovascular ischemia could be related to the extent of preexisting, chronic cerebrovascular injury marked by leukoaraiosis and measured on MRI as WMHV. Severity of leukoaraiosis has been shown to affect infarct growth in patients with acute ischemic stroke and inversely correlate with functional outcome.^{10,18,19} A greater susceptibility of “tissue-at-risk” for progression to infarction could arise from impaired mechanisms of cerebral perfusion in those patients with the greatest burden of WMH,^{20,21} or alternatively could be the result of chronic mechanisms of injury to the cerebral vasculature.²² Whether the injury reflected by WMH affects the reactivity of vessels or their collective structural integrity is unknown;^{23,24} however, it ultimately leads to infarction of

Table 2. Multivariate Predictors of Acute Ischemic Stroke vs Transient Ischemic Attack*

	OR	95% CI	P Value
WMHV	2.19	1.27–3.77	0.005
Hyperlipidemia	0.28	0.09–0.84	0.02
Statin use	0.18	0.06–0.52	0.002

*Effect sizes expressed as odds of AIS vs TIA. IQR indicates interquartile range; WMHV, white matter hyperintensity volume.

Table 3. Multivariate Predictors of Acute Ischemic Stroke vs Transient Ischemic Attack: Sensitivity Analysis Based on the Hyperlipidemia vs Statin Use Status*

	N	OR	95% CI	P Value
WMHV	150	2.07	1.21–3.53	0.008
HL–/statin use–	62	1.0	Ref	Ref
HL–/statin use+	11	0.44	0.07–2.96	0.41
HL+/statin use–	37	0.46	0.12–1.73	0.25
HL+/statin use+	22	0.27	0.05–0.47	0.001

*Effect sizes expressed as odds of AIS vs TIA. IQR indicates interquartile range; HL, hyperlipidemia; ref, reference category; WMHV, white matter hyperintensity volume.

cerebral tissue that was initially only ischemic.¹⁰ Prospective studies of the role of leukoaraiosis in cerebrovascular ischemia, including advanced studies of cerebral perfusion, may further elucidate this complex interaction.

The definition of transient cerebrovascular ischemia has evolved over the years¹ as the ability to assess cerebral tissue state during the episode of neurological dysfunction improved with advancement of neuroimaging techniques.⁴ In this study, we defined TIA based on the latest consensus,¹ and the final diagnosis of TIA in our cohort was based on the confirmed absence of acute cerebral ischemia on diffusion-weighted MRI. We used neuroimaging and chart review to exclude any potential TIA mimics (seizure, meningitis, acute manifestation of neurodegenerative diseases, or recrudescence of preexisting cerebrovascular disease in the setting of systemic illness). Although DWI is the gold standard for confirming acute infarction, it is possible that some of our TIA cases may have had irreversible infarction not detected on DWI. These clinically silent infarcts, however, are likely to have been extremely small.

The role of HL in cerebrovascular disease and stroke is currently undergoing investigation. Whereas elevated serum lipids increase risk of ischemic stroke²⁵ and use of statins for lipid-lowering is now universally accepted for secondary stroke prevention,^{26,27} the effects of HL on long-standing injury to the brain are controversial, especially in disorders of small cerebral vasculature.^{13,28,29} We previously demonstrated that diagnosis of HL before acute ischemic stroke was associated with decreased burden of WMH in patients with AIS;¹³ however, considerations of low power and high colinearity between the diagnosis of HL and statin use status precluded any further inference with regard to the effect of HL on WMH burden. In the present study, the apparent protective effect of HL on WMH burden emerges through its association with statin use. In fact, those patients previously diagnosed with HL and who were also receiving statins had the lowest odds of stroke vs TIA. Therefore, as a surrogate marker of statin use before a cerebrovascular event, HL may be independently protective from cerebral infarction.

Several other vascular risk factors have been previously implicated in progression of transient ischemia to cerebral infarct, including advanced age, HTN, and DM.^{5,9,30} Age is one of the most powerful predictors of WMH burden among healthy adults^{31,32} as well as the patients with AIS;^{13,17} therefore, we carefully matched the TIA subjects in this study with controls by age to minimize confounding. Neither diagnosis of HTN nor DM appeared to have effect on diagnosis of TIA vs AIS in this study. The mechanisms of cerebral small vessel disease are still unclear.^{33,34} In patients with ischemic stroke, risk factors affecting severity of WMH appear to differ from those in population-based cohorts.^{13,17} Provided that susceptibility of the brain to ischemia leading to cerebral infarct as opposed to TIA might be mediated by WMH severity, the effects of HTN and DM on progression of transient ischemia to stroke might be obscured in this analysis based on the neuroimaging evidence of cerebral tissue state.

This study is limited by its small size and its retrospective nature. Although our nested case-control design enabled us to control for age, the most well-known determinant of WMH

burden, and cases and controls appear to be closely matched based on the admission NIHSS score (TIA vs “minor stroke”), we were not able to control for all potential confounders, including variation of clinical symptomatology, variability in the degree of collateral circulation, and additional characteristics that may be important, such as history of cerebrovascular events, the degree of functional recovery in AIS controls, or time to MRI measured in minutes per hour between cases and controls.

Conclusion

In patients presenting with symptoms and signs of acute cerebral ischemia, severity of WMH is an independent predictor of the development of irreversible cerebral infarction. These findings suggest that chronic injury to small cerebral vasculature measured on MRI as burden of WMH may play an important role as a marker of susceptibility to stroke or progression to stroke in the setting of transient cerebral ischemia.

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